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Efficacy and safety of tafenoquine for malaria chemoprophylaxis (1998-2020): A systematic review and meta-analysis

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Abstract: **BACKGROUND** In 2018, tafenoquine was approved for malaria chemoprophylaxis. We evaluated all available data on the safety and efficacy of tafenoquine chemoprophylaxis. **METHODS** This systematic review followed the PRISMA guidelines and was registered on PROSPERO (CRD42019123839). We searched PubMed, Embase, Scopus, CINAHL and Cochrane databases. Two authors (JDM, PS) screened all papers. **RESULTS** We included 44 papers in the qualitative and 9 in the quantitative analyses. These 9 randomized, controlled trials included 2495 participants, aged 12-60 years with 27.3% women. Six studies were conducted in Plasmodium spp.-endemic regions; two were human infection studies. 200 mg weekly tafenoquine and higher dosages lead to a significant reduction of Plasmodium spp. infection compared to placebo and were comparable to 250 mg mefloquine weekly with a protective efficacy between 77.9 and 100% or a total risk ratio of 0.22 (95%-CI: 0.07-0.73; $p = 0.013$) in favour of tafenoquine. Adverse events (AE) were comparable in frequency and severity between tafenoquine and comparator arms. One study reported significantly more gastrointestinal events in tafenoquine users ($p = 0.001$). Evidence of increased, reversible, asymptomatic vortex keratopathy in subjects with prolonged tafenoquine exposures was found. A single, serious event of decreased macular sensitivity occurred. **CONCLUSION** This systematic review and meta-analysis of trials of G6PD-normal adults show that weekly tafenoquine 200 mg is well tolerated and effective as malaria chemoprophylaxis focusing primarily on Plasmodium falciparum but also on Plasmodium vivax. Our safety analysis is limited by heterogeneous methods of adverse events reporting. Further research is indicated on the use of tafenoquine in diverse traveller populations.

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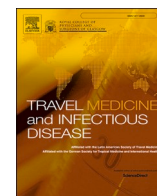


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Original article

Efficacy and safety of tafenoquine for malaria chemoprophylaxis (1998–2020): A systematic review and meta-analysis

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ABSTRACT

Background: In 2018, tafenoquine was approved for malaria chemoprophylaxis. We evaluated all available data on the safety and efficacy of tafenoquine chemoprophylaxis.**Methods:** This systematic review followed the PRISMA guidelines and was registered on PROSPERO (CRD42019123839). We searched PubMed, Embase, Scopus, CINAHL and Cochrane databases. Two authors (JDM, PS) screened all papers.**Results:** We included 44 papers in the qualitative and 9 in the quantitative analyses. These 9 randomized, controlled trials included 2495 participants, aged 12–60 years with 27.3% women. Six studies were conducted in *Plasmodium* spp.-endemic regions; two were human infection studies. 200 mg weekly tafenoquine and higher dosages lead to a significant reduction of *Plasmodium* spp. infection compared to placebo and were comparable to 250 mg mefloquine weekly with a protective efficacy between 77.9 and 100% or a total risk ratio of 0.22 (95%-CI: 0.07–0.73; $p = 0.013$) in favour of tafenoquine. Adverse events (AE) were comparable in frequency and severity between tafenoquine and comparator arms. One study reported significantly more gastrointestinal events in tafenoquine users ($p \leq 0.001$). Evidence of increased, reversible, asymptomatic vortex keratopathy in subjects with prolonged tafenoquine exposures was found. A single, serious event of decreased macular sensitivity occurred.**Conclusion:** This systematic review and meta-analysis of trials of G6PD-normal adults show that weekly tafenoquine 200 mg is well tolerated and effective as malaria chemoprophylaxis focusing primarily on *Plasmodium falciparum* but also on *Plasmodium vivax*. Our safety analysis is limited by heterogenous methods of adverse events reporting. Further research is indicated on the use of tafenoquine in diverse traveller populations.

1. Introduction

Malaria caused 228 million infections and 405,000 deaths in 2019 [1]. Persons living in endemic areas are at high risk of infection, as are travellers visiting such areas [2]. Antimalarial drugs constitute an important pillar of malaria prevention, together with individual measures against mosquito bites [2]. Since malaria chemoprophylaxis is

generally taken by healthy travellers, it is important that such regimens are effective, safe, well tolerated, and offer convenient dosing schedules ensuring good adherence [3]. [4,5].

Chemoprophylaxis against malaria has long been dominated by drugs active only against the asexual blood stages of the plasmodia responsible for the acute clinical attack. These suppressive agents alone do not prevent the latent malaria (typical of *Plasmodium vivax* and

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Plasmodium ovale) due to dormant hepatic stages called hypnozoites that can occur in the weeks and months following travel [6]. In contrast, causal prophylaxis, kills all hepatic plasmodia either in the primary liver phase or the dormant liver phase “hypnozoites”. In this way, causal chemoprophylaxis prevents both acute and delayed malaria attacks during and after travel.

In 2018, a novel antimalarial drug, tafenoquine, was approved in the US and Australia [7,8]. Tafenoquine is an 8-aminoquinoline from the late 1970s [9,10]. Its main advantage compared to other antimalarials is its effects on all human malaria parasite stages and species at therapeutic dosing (Fig. 1) [7,11]. Use in anti-relapse therapy places tafenoquine alongside another 8-aminoquinoline, primaquine, which for over 60 years had been the only effective therapy against latency in the hypnozoite-bearing species [7,12]. Even though, primaquine is considered a robust anti-relapse therapy and radical cure for those infections, its safe and efficacious use as a causal chemoprophylactic agent was demonstrated but not widely practiced [13,14]. Unlike primaquine, tafenoquine has a prolonged half-life of 12–17 days [14–16] enabling weekly dosing for chemoprophylaxis [14]. As with primaquine, tafenoquine comes with potentially dangerous haemolytic toxicity in G6PD-deficient patients and thus requires G6PD testing prior to use. Pregnancy contraindicates tafenoquine use and tafenoquine is not yet proven safe as chemoprophylaxis for those aged <18 years, [17]. The duration of chemoprophylactic dosing is limited to 6 months [18]. Tafenoquine represents an important advance in the prevention of travellers' malaria in promising improved adherence and as a solitary chemoprophylactic agent preventing both acute and delayed attacks of malaria.

This systematic review evaluated several randomized, double-blind, placebo-controlled, and/or active controlled studies eligible for a subsequent meta-analysis (Table 1). Reviews have already been conducted, addressing the safety and efficacy of tafenoquine [19,20]. In contrast to these studies, this systematic review scrutinizes efficacy and safety data for primary chemoprophylaxis only and includes studies, that have not previously been analysed in a meta-analysis.

2. Methods

We conducted the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. Details of the protocol for this systematic review were registered on PROSPERO (CRD42019123839) [22].

The electronic literature search included all past studies until June 6th, 2020 using searches of the electronic databases PubMed, Embase, Scopus, CINAHL, and Cochrane Library. The search query combined tafenoquine with several synonyms (including WR238605 and etaquine) to identify all potential studies and was developed by JM and PS (Appendix A). After duplicates were removed by JM using Endnote [23], two authors (JM and PS) screened independently all titles and abstracts according to inclusion and exclusion criteria (Table 2). After the screening, a full-text assessment was performed by two authors (JM and PS) for eligibility. At any selection step, disagreements between reviewers were resolved by consensus. Additional records were obtained by contacting study authors and/or study sponsors.

For the meta-analysis, we included randomized clinical trials only. However, for the qualitative assessment, we used other types of records, such as pre-specified analysis plans (Fig. 2). Concerning chemoprophylactic efficacy, we only included studies, that administered tafenoquine before malaria exposure. Safety data were extracted when drug intake duration was longer than one week. This duration was chosen to best display adverse events that can occur during prolonged use, rather than short use as in radical cure or anti-relapse therapy. The records were included independent of participant characteristics (e.g. naïve/non-naïve, age, sex) outcome measurement method, length of follow-up, published language, publication date, as well as tafenoquine dosage and intake frequency.

Two authors (PS and JM) conducted data extraction according to the DECIMAL guide [24]. While one reviewer (JM) extracted data from included studies, the second one (PS) checked all extracted data. Disagreements were discussed and resolved by consensus.

The extracted information is detailed in Tables 1, 3–7, appendix B

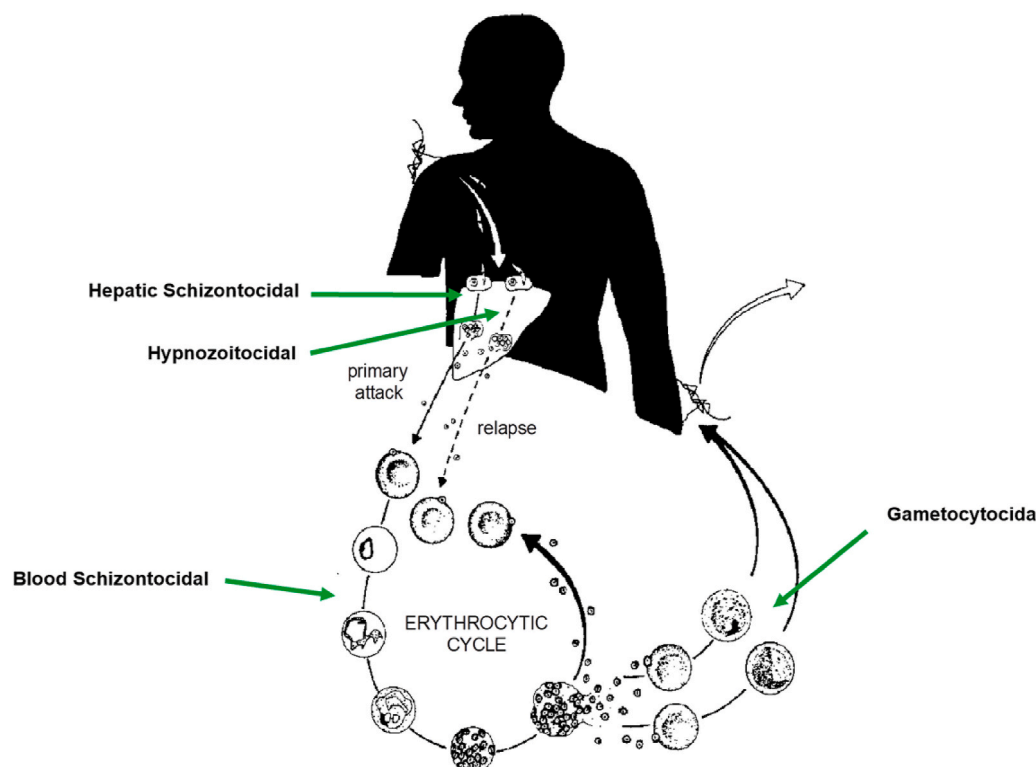


Fig. 1. Sites of tafenoquine action in the *Plasmodium* species human life cycle. Adapted from Schlagenhauf, Funk: PDQ Travelers' Malaria.

Table 1

Overview study characteristics. AC = Active Comparator (250 mg Mefloquine), BC = bicentric, DB = Double-Blind, HC = Human Challenge Study, MC = monocentric, NA = Not Applicable, NR = Not Reported, PC = Placebo-Controlled, R = Randomized, SP = study phase.

Study	Study design	Assessed parameters	Study location	Population	Endemic plasmodia	No. of participants for efficacy analysis (male, %)	No. of participants for safety analysis (male, %)	No. of arms	Duration of drug administration	Duration of follow-up	Preliminary malaria eradication
Lell 2000	R, DB, PC, MC, SP2	efficacy	Lambaréné, Gabon	non-naive, local, healthy students	<i>P. falciparum</i>	352 (47.07%)	NA (NA)	5	3 days (loading dose only)	10 weeks	with halofantrine
Shanks 2001	R, DB, PC, MC, SP2	efficacy and safety	Ndori Village near Lake Victoria, Kenya	non-naive, healthy adults	<i>P. falciparum</i>	235 (60.85%)	235 (60.85%)	4	13 weeks	4 weeks	with halofantrine
Hale 2003	R, DB, AC, PC, MC, SP 2	efficacy and safety	Kassena-Nankana district, Ghana	non-naive, health, adult residents	<i>P. falciparum</i>	509 (65.42%)	513 (NR)	6	12 weeks	4 weeks	with quinine sulfate, doxycycline, primaquine
Walsh 2004	R, DB, PC, MC, SP2	efficacy and safety	Nam Yun District, Ubol Ratchatani Province, Thailand	healthy, Thai soldiers	<i>P. falciparum</i> and <i>P. vivax</i>	205 (100%)	205 (100%)	2	26 weeks	13 weeks	with artesunate, doxycycline
Leary 2009	R, DB, PC, BC, SP1	safety	Bethesda (MD), USA and Slough (Berkshire) UK	healthy adults	NA	NA (NA)	120 (60.83%)	2	24 weeks	NR	NA
Nasveld 2010	R, DB, AC, MC, SP3	efficacy and safety	Bobonaro District, Timor Leste	naive, healthy australian soldiers	<i>P. falciparum</i> and <i>P. vivax</i>	651 (NR)	654 (96.64%)	2	26 weeks	24 weeks	NR
Stoute 2017	R, DB, AC, PC, MC, SP2	efficacy and safety	Nyanza Province, Kenya	non-naive, healthy adults	NR	300 (65%)	306 (NR)	3	24 weeks	4 weeks	with halofantrine
Brueckner 1998	R, DB, PC, HC, MC, SP2	efficacy	NR	naive, healthy adults	NA ((exposure to <i>P. falciparum</i>))	6 (NR)	NA (NA)	2	1 day	9.3 weeks	NR
McCarthy 2018	R, DB, PC, HC, MC, SP1b	efficacy and safety	Qpharm Pty Ltd, Brisbane, Australia	naive, healthy adults	NA (exposure to <i>P. falciparum</i>)	16 (37.5%)	16 (37.5%)	2	2 weeks	3.5 weeks	NR

and E. For the safety analysis, serious and non-serious adverse events, and laboratory results from published records were extracted. Adverse events were extracted as a total and as individual symptoms; these individual symptoms were then grouped according to the Medical Dictionary for Regulatory Activities (MedDRA® version 22.0). When a symptom could be categorized into several groups, it was assigned to the most suitable group. When two or more *Plasmodium* species were detected, the combined incidence was extracted for meta-analysis.

For the efficacy data, meta-analyses were performed. The effect of prophylaxis was expressed as risk ratios (RR) with 95% confidence intervals (CIs) comparing the incidence of parasitaemia in the group receiving tafenoquine prophylaxis with the placebo or mefloquine group. Pooled analyses were conducted with a random effects model using logit transformed proportions, with subsequent back-transformation to the original scale. To avoid numerical issues, zero events adjustments were applied by adding a constant of 0.5 for computing both the proportion and the corresponding sampling variance for studies with zero events in at least one cell.

Results were visualised in forest plots with the estimate and 95% CIs for the pooled RR given by the black diamond. The RR of each trial and

95% CIs are indicated by individual squares and horizontal bars. The size of the square is proportional to the weight given to each individual trial by random effects model pooling the outcomes. The. Additionally, Cochrane's Q-test for heterogeneity with corresponding p-value and I^2 for the total heterogeneity over the total variability were computed. A p-value of <0.05 of the heterogeneity tests was indicative of heterogeneous outcomes. All meta-analyses were performed in the R system for statistical computing (version 4.0.0), using the package metafor (version 2.4.0) [25].

The risk of bias was assessed by two authors (PS and JM) using the revised Cochrane risk of bias tool for randomized trials (RoB 2) [26]. According to RoB 2, missing outcome data of >5% were considered as high. Discrepancies were discussed and resolved by consensus.

3. Results

A total of 44 publications were selected for **qualitative** analysis, of which 9 were included for **quantitative** analysis of efficacy (n = 8) and safety (n = 7) (Fig. 2). After full text assessment of 82 records, one additional record for inclusion was identified: An Australian New

Table 2
Eligibility criteria for screening and full-text analysis.

	Criteria for inclusion in qualitative and/or quantitative analysis	Criteria for inclusion in discussion	Criteria for exclusion
Subjects	Primary chemoprophylaxis of tafenoquine regarding safety, tolerability and/or efficacy	Safety studies including single dosages that focus on <ul style="list-style-type: none"> ophthalmic, haemolytic, ECG, neurotoxic adverse events Studies including single dosages concerning: <ul style="list-style-type: none"> pharmacokinetics drug-drug interaction sex differences Animal based studies (in vivo) if other inclusion criteria for qualitative and/or quantitative analysis are met	<ul style="list-style-type: none"> anti-relapse-therapy post-exposure prophylaxis terminal prophylaxis radical cure analytical methods molecular mechanisms pharmacodynamics in vitro studies non-malarial diseases
Record types	<ul style="list-style-type: none"> clinical trial, RCT clinical trial protocol human challenge studies no study phase restriction trial registries reviews letters to the editor approval announcements 		<ul style="list-style-type: none"> Expert opinion review protocol
Other criteria	No language exclusion Studies with other topics but same study population as trials included for qualitative and/or quantitative		

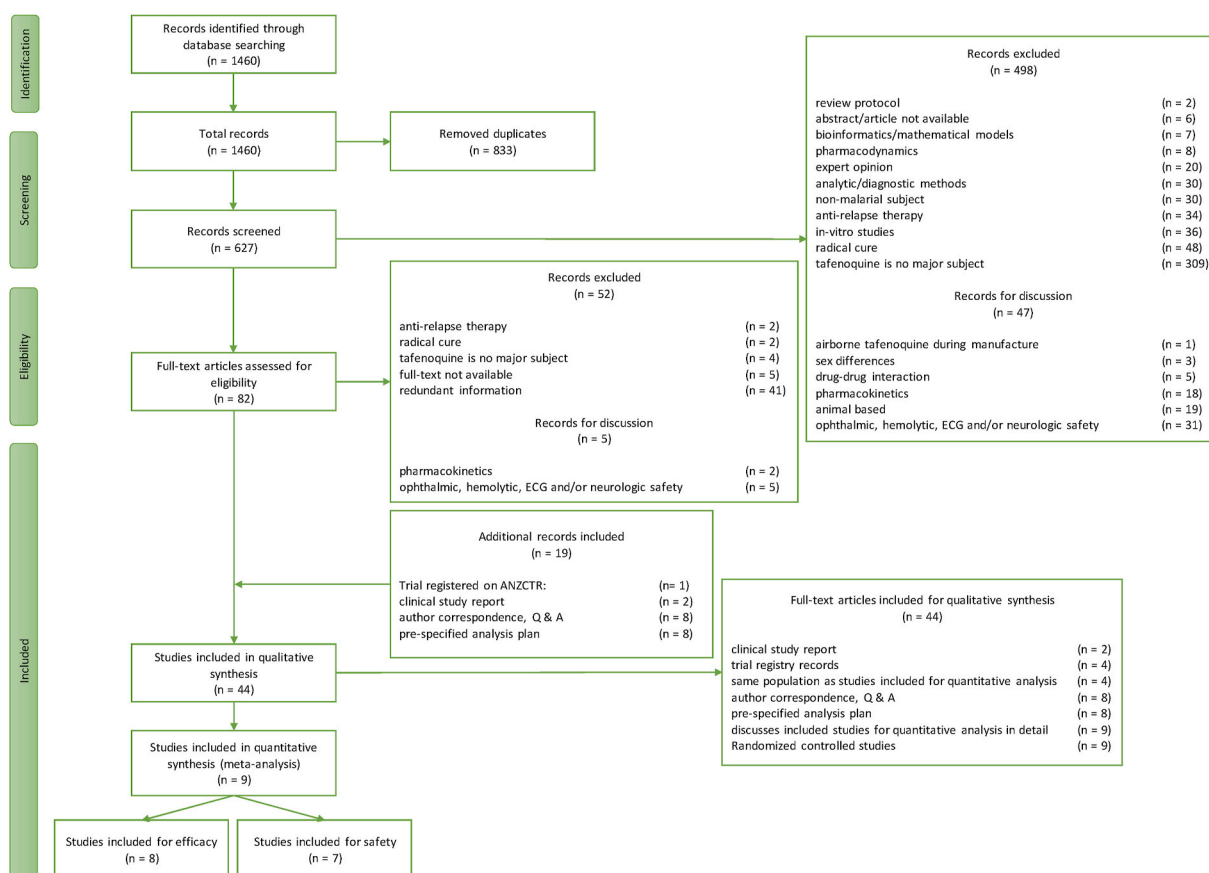


Fig. 2. Flow chart for the selection of records. “Records for discussion” are records, that were excluded but might be useful for the discussion part of this paper. All excluded records were categorized according to eligibility criteria. One study can be present in two or more categories within a list, except when tafenoquine was no major subject, there was non-malarial subject, it was a review protocol, the article/study was not available or there was only redundant information already covered in an included record. For example, when tafenoquine was no major subject, it was only categorized into “tafenoquine is no major subject”. The records listed in “full-text articles included for qualitative synthesis” are only mentioned ones per category.

Zealand Clinical Trials Registry record, which was the source of the included record from the International Clinical Trials Registry Platform [27]. Another 18 records were included after correspondence with study authors and GlaxoSmithKline (GSK).

All 9 studies included for **quantitative** analysis were randomized controlled studies. The duration of drug intake was between 1 day and 6 months, while the follow-up monitoring lasted between 9 weeks and 9 months. Overall, 2495 participants (female $n = 669/2449$; 27.3%) were randomized in all 9 studies, while 2274 participants (female $n = 622/2329$; 26.7%) were eligible for efficacy and 2049 participants were eligible (female $n = 452/2039$; 22.2%) for safety analysis. Since the proportion of sex was only given once for the intend-to-treat or per-protocol population per study, the number differs slightly when the other population was used for analysis. Different participant inclusion and exclusion criteria were used (Appendix B). All participants with a glucose-6-phosphate dehydrogenase (G6PD) deficiency, pregnancy, breastfeeding, and clinically relevant abnormal laboratory or physical examination were excluded per investigation protocols.

Most of the studies were monocentric; only Leary et al. conducted a two-centre study (Table 1) [28]. The study authors performed either intention-to-treat, modified intention-to-treat, and/or per-protocol population analyses. Study interventions varied from oral single dosages (600 mg tafenoquine base), only loading dosages (25–400 mg tafenoquine base, daily for 3 days) to weekly (25–400 mg tafenoquine base), and monthly dosages (400 mg tafenoquine base). Active control arms were always weekly 250 mg mefloquine (Table 3). Definitions of efficacy outcome points always included newly detected positive blood smears during prophylactic study phase except in McCarty et al., 2018 where qPCR was employed for malaria detection [29]. All studies included for efficacy analysis screened all participants periodically, independently of symptoms. Safety outcome points varied greatly among the included studies (Table 4). All included RCT's evaluated adverse events, but not all were included in our safety analysis, since the duration of drug intake in 2 RCT's was shorter than a week [30,31]. The timing of outcome measures varied between daily and monthly evaluations; they also varied within a study for different outcome parameters. Follow-up time depended on the endemic *Plasmodium* species; being prolonged if *Plasmodium vivax* were present (Table 1).

Bias assessments were done for each safety and efficacy analysis shown in Figs. 3–5. The detailed bias assessment is described in Appendix C.

Efficacy analysis: Eight studies were analysed for efficacy (Table 5). Seven of them compared tafenoquine to placebo while Nasveld et al.,

2010 only used an active comparator [32]. An active comparator was also used by Hale et al., 2003 and Stoute et al., 2017 (Table 3) [33,34]. Since placebo arms are needed for calculating protective efficacy, the published paper by Nasveld et al., 2010 was followed by Dow et al., 2014, a retrospective study to assess protective efficacy using an estimated malaria attack rate [35]. While six studies were RCT's conducted in endemic regions exposed to malaria infection, two were human challenge studies using intravenous injection of viable *P. falciparum*-infected erythrocytes or viable sporozoites from feeding mosquitos (Table 1) [29,31]. Most studies described an exposure to *P. falciparum*, while two studies also stated *P. vivax* as an additional possible infectious agent.

While sex differences were not analysed in all included RCT's, Hale et al., 2003 detected a significant interaction between treatment efficacy and body weight ($P < 0.001$). Blood smears were more likely to be positive among heavier subjects [33].

Tafenoquine vs. placebo: Most analysed studies favour tafenoquine over placebo for malaria chemoprophylaxis. Three studies, however, did not show evidence for a reduction in acquired malaria infection (Fig. 6). Two of those three studies only administered tafenoquine during a narrow time frame at the start with 600 mg tafenoquine in total (Table 3) [30,31,34,36]. After correspondence with GSK about the high failure rate reported by the third one, Stoute et al., 2017, they explained that “there were issues identified with the quality of the slide reading, resulting in false positives” [36].

For the currently approved tafenoquine dosages of 200 mg weekly, we calculated a total RR of 0.22 (95%-CI: 0.07–0.73; $p = 0.013$) in favour of tafenoquine (Fig. 6) and for all included dosages above 200 mg independent of frequency a RR of 0.20 (95%-CI: 0.10–0.39; $p < 0.0001$). Besides Stoute et al., 2017, the protective efficacy of tafenoquine for the ones that favour tafenoquine ranged between 85.6% and 100%, while Stoute et al., 2017 calculated a protective efficacy of 77.9% (Table 5) [34]. Higher doses of tafenoquine resulted in protective efficacies of 89% (400 mg, weekly) and 97% (400 mg, monthly), respectively, and RR of 0.12 (95%-CI: 0.05–0.25) and 0.03 (95%-CI: 0.00–0.23), respectively (Table 5, Fig. 6).

Both human challenge studies did not report any protective efficacy, but tafenoquine drug failures of 0% and 25% in McCarthy et al., 2018 and Brueckner et al. respectively (Table 5) [29,31]. Both performed a single challenge on day 3 and day 1 after the last tafenoquine dosage, respectively [29,31].

Tafenoquine vs. mefloquine: Three studies used mefloquine as an active comparator (Table 3) [32–34]. Hale et al., 2003 states, that their comparison of tafenoquine to mefloquine could only be descriptive, due to low power. Nevertheless, the protective efficacy of tafenoquine and mefloquine were similar (Table 5). The retrospective study conducted by Dow et al., 2014 and the clinical study by Stoute et al., 2017 did not show evidence for a difference in protective efficacy by tafenoquine or mefloquine [34,35]. Our RR analysis resulted in a pooled RR of 0.95 (95%-CI: 0.87–1.04, $p = 0.26$), however, does support those numbers and shows no evidence for favouring towards tafenoquine or mefloquine (Fig. 7).

Safety analysis: Seven studies were analysed for safety (Table 1). Six of them compared tafenoquine to placebo while one used an active comparator (Table 1) [33,34]. As for the efficacy analysis, our safety analysis only included dosages from 200 mg and higher regardless of the frequency but with a duration of at least one week.

Studies included in the safety analysis reported comparable adverse event rates between prophylaxis groups, with some exceptions. Walsh et al., 2004 reported a significant higher number of gastrointestinal complaints among tafenoquine recipients ($p \leq 0.001$, Fisher's exact test; placebo $n = 24/101$, 23.8%; tafenoquine monthly 400 mg $n = 74/104$, 71.2%; Fig. 8, Appendix E) than among placebo recipients [37]. Leary et al., 2009 noted a higher incidence of nausea in the tafenoquine than in the placebo group, but a higher incidence of headache in the placebo than in the tafenoquine group (Fig. 9) [28]. Furthermore, Leary et al.

Table 3

Study dosages. Loading dose always was always done except “single dose” is mentioned. A Loading dose included the displayed dosage on day one, two and three.

Study	Study arms		
	tafenoquine	mefloquine	placebo
Lell 2000	25 mg, 50 mg, 100 mg, 200 mg (loading dose only)	–	loading dose only
Shanks 2001	200 mg (loading dose only with weekly placebo), 200 mg (weekly), 400 mg (weekly)	–	weekly
Hale 2003	25 mg, 50 mg, 100 mg, 200 mg (weekly)	250 mg (weekly)	weekly
Walsh 2004	400 mg (monthly)	–	monthly
Leary 2009	200 mg (weekly)	–	weekly
Nasveld 2010	200 mg (weekly)	250 mg (weekly)	–
Stoute 2017	200 mg (weekly)	250 mg (weekly)	weekly
Brueckner 1998	600 mg (single dose)	–	Single dose
McCarthy 2018	200 mg (weekly)	–	weekly

Table 4

Differences in adverse events reporting. NS = not specified, NR = not reported, S = solicited, US = unsolicited.

Study	Adverse events reporting	AE assessment frequency	Solicited, unsolicited	Definition of serious adverse events by study authors
Lell 2000	"The volunteers were urged to report to investigators if any medical problem occurred."	Once weekly	S	NR
Shanks 2001	"On a weekly basis (done when the subjects received their medication), volunteers were questioned regarding adverse events, a malarial blood smear was performed, and a review of concomitant medication was performed."	Once weekly	S	A serious adverse drug event was any event that was fatal, life threatening, permanently disabling, required subject hospitalization, or was a congenital abnormality, cancer, or overdose. In addition any event which the study staff regarded as serious or that suggested any significant hazard, contraindication, side effect or precaution that might have been associated with the use of the drug was to be reported as a serious event
Hale 2003	"[...] complaints or symptoms were reported to the study-team physicians. Subjects with physical complaints were examined by a study physician the next day or on an emergent basis, as needed."	3 times a week	S	NR
Walsh 2004	"Adverse events were recorded [...] according to a predefined coded checklist of the most commonly expected AEs."	Daily during the 3-day loading dose and then at approximately 24 h after each dose.	S	Serious AEs were defined as those that required hospital admission.
Leary 2009	"Adverse event reporting, pregnancy testing, and concomitant medications review were conducted at screening, weekly throughout the dosing period, and at follow-up."	Once weekly.	S	Serious adverse events were defined as events that resulted in death, were life-threatening, required hospitalization, prolongation of an existing hospitalization, or resulted in incapacity or disability. The protocol defined clinically significant renal and ophthalmic events as serious AEs to facilitate expedited reporting.
Nasveld 2010	"Adverse events monitoring was supplemented by review of subjects' medical records. Disclosure of adverse events was elicited by the investigator asking the subject the nonleading question, "Do you feel differently in any way since starting the new treatment?" A Study physician assessed the level of relationship of any adverse event on the basis of the subject's response and any temporal association and/or known adverse events as mild (not affecting daily activities), moderate (with some interference in daily activities), and severe (when daily duties could not be completed). A causal relationship to the study drug was judged by the physician to be not related, unlikely, suspected, or probable."	Prophylactic phase: At loading stage, week 4, 8, 16 and 26. Follow-up phase: Week 2 and 12	S	NR
Stoute 2017	NR	NR	S	NR
Brueckner 1998	Volunteers were questioned periodically for symptoms	Periodically.	S	NR
McCarthy 2018	"Safety assessment included evaluation of AEs, AEs of special interest (AESI), physical examination, vital signs, clinical laboratory measurements [...] and standard 12-lead ECGs (at screening only)."	On days 4–9, 11–12 and 14–16.	S	NR

reported five cases of "treatment emergent myalgia/intercostal myalgia in tafenoquine persons, compared with none in the placebo group" with abnormal creatinine phosphokinase (CPK) in two of them [28]. Shanks et al., 2001 described a higher incidence of gastrointestinal adverse events in participants who received 400 mg weekly as well but also more dermatological events across all tafenoquine arms than in the placebo group [38]. Stoute et al., 2017 shows a higher incidence trend in back pain among tafenoquine recipients than in placebo and mefloquine recipients (Fig. 9) [34]. Nasveld et al., 2010 observed no evidence for a difference in any adverse events between tafenoquine and mefloquine groups, regardless of whether they were related to study drug or not [32]. In all studies, except for one syncope, no cardiac adverse events and no evidence for ECG changes were reported.

Study discontinuation: While subject withdrawal across studies were zero to 25.5% in any tafenoquine study arm (placebo 0.0–11.5%; mefloquine 2.0%–5.6%), subject withdrawal due to adverse events ranged between zero to 9.7% (placebo: 0.00–5.1%; mefloquine: 0.0–1.9%) (Table 6). Even though Hale et al., 2003 reported study discontinuation across all study arms (83/509, 16.31%), they were not included since no data per study arm was provided by the authors [34].

Serious adverse events: A total of 24/1000 (2.4%) serious adverse

events were reported in all tafenoquine groups using dosages of 200 mg or higher, 2/309 (0.6%) in the mefloquine groups and 18/400 (4.5%) in the placebo groups (Table 6). Only one serious adverse event in the tafenoquine arm, but none in the mefloquine and placebo arms, was considered possibly related to the study drug. That possibly related serious adverse event was a decrease in macular sensitivity recorded by Leary et al., 2009 [28]. One serious adverse event reported by Hale et al., 2003 occurred in a non-randomized participant, which is why that participant was not considered for the safety analysis [33]. Nasveld et al., 2010 and Shanks et al., 2001 did not explicitly mention any serious adverse events. However, for Shanks et al., 2001, we extracted them from the clinical study report, which was provided by GSK [32, 38].

Laboratory adverse events: Most laboratory values, if abnormal, showed only minor and transient changes. Those that showed differences were haemolytic parameters, bilirubin, liver enzymes, kidney parameters and methaemoglobin (Table 7).

Changes in haemoglobin and haemolytic parameters were generally more common in tafenoquine recipients, however, no evidence for a difference between arms were reported [28,29,32–34,38]. Increased bilirubin values were only mentioned by two studies, mainly detected in

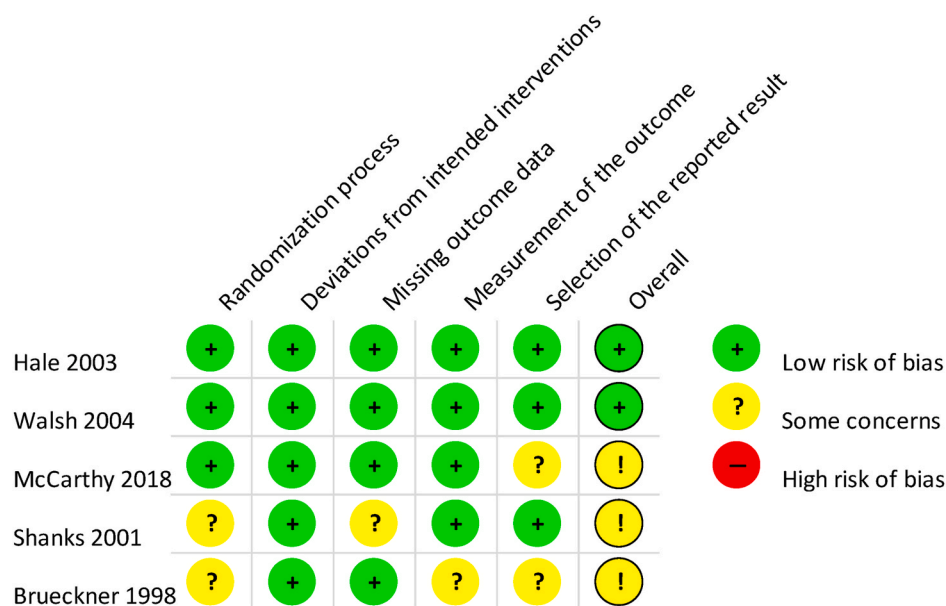


Fig. 3. Risk of bias for included studies concerning efficacy and studies with intention-to-treat analyses.

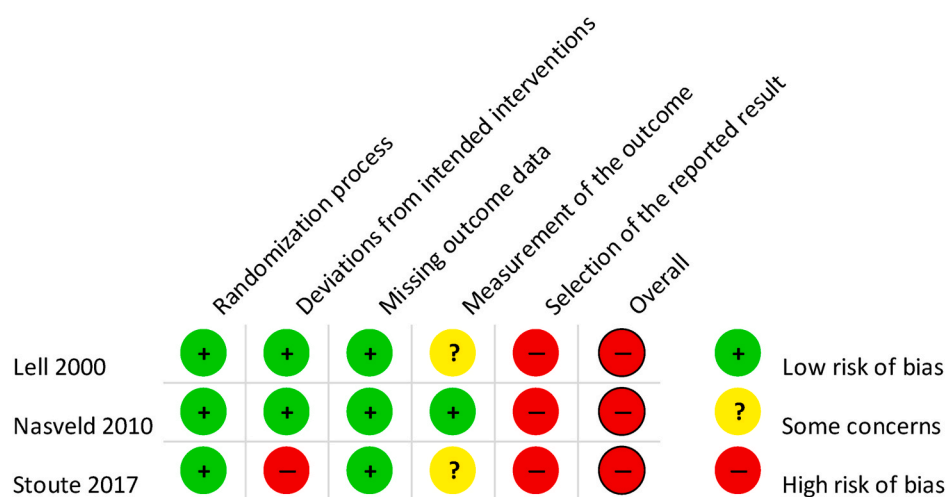


Fig. 4. Risk of bias for included studies concerning efficacy and studies with per-protocol analyses.

tafenoquine arms, but significant differences between arms were not reported [29,32]. Elevated alanine aminotransferase (ALT) levels were reported by two studies, they were more common in tafenoquine arms, mostly transient and not associated with any symptoms. The exception was one participant, in which high ALT levels were caused by a chronic hepatitis B infection [33,37]. Three studies described elevated serum creatinine values, even though they were generally more seen in tafenoquine arms, no significant differences were reported [28,32,37]. Three studies reported increased methaemoglobin values in tafenoquine arms compared to placebo [32,37,38].

Ophthalmologic adverse events: Ophthalmological adverse events were reported by three studies [28,32,34]. While Nasveld et al., 2010 and Leary et al., 2009 did additional eye examinations, Stoute et al., 2017 only reported conjunctivitis as an adverse event (placebo $n = 13/101$; 12.9%, tafenoquine $n = 12/104$; 11.5%, mefloquine $n = 7/101$; 6.9%). Nasveld et al., 2010 only assessed a subgroup (77 on tafenoquine, 21 on mefloquine) for ophthalmic adverse events. They detected a high proportion of vortex keratopathy (corneal deposits) in tafenoquine recipients only ($n = 69/74$; 93.2%; mefloquine $n = 0/21$; 0.0%), however, these changes were not associated with any visual disturbances. After

one year of follow-up, every vortex keratopathy had dissolved [32]. The ophthalmologic adverse events were one of Leary et al., 2009's primary endpoint. They did several ophthalmological tests, which yielded no differences in night vision, macular function, contrast visual acuity, colour vision, peripheral visual field, or retinal morphology. However, Leary et al., 2009 observed a non-significant newly occurring corneal deposits in tafenoquine users ($n = 15/60$, 25.0%) versus placebo group ($n = 4/25$, 16.0%) ($p = 0.5683$, Fisher's exact test). While in 14 tafenoquine receiving participants, corneal deposits resolved within 12 weeks of onset, all 4 persons who received placebo, corneal deposits resolved within 6 weeks of onset. All corneal deposits resolved within 24 weeks post-dosing. One tafenoquine recipient had a mild decrease in macular sensitivity, which was considered to be possibly related to study drug and was withdrawn from the study, this mild decrease resolved spontaneously. Retinal abnormalities were detected in both study arms once (tafenoquine and placebo). A single area of retinal hyperpigmentation in a tafenoquine recipient was detected, which did not change after 11 months cessation of therapy. The retinal abnormality in the placebo recipient resolved within 2 months [28].

Nervous system and psychiatric adverse events (AE): No study

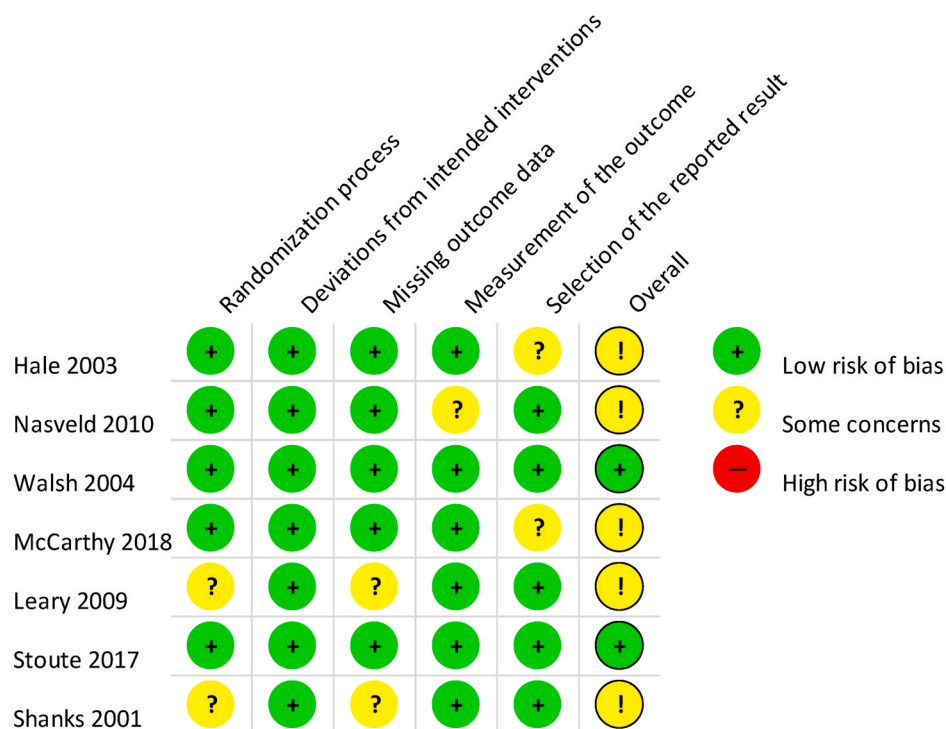


Fig. 5. Risk of bias for included studies concerning safety and studies with intention-to-treat analyses.

Table 5

Overview of analysed study arms including duration of drug administration and reported protective efficacy. Loading doses were always done if “once” is not mentioned and they were done on day one, two and three with the mentioned dosages. ITT = intention-to-treat, mITT = modified intention-to-treat, pp = per-protocol, taf = tafenoquine, mef = mefloquine, *protective efficacy calculated by Dow et al. 2014.

Study	number of participants for efficacy analysis	number of arms	analysis based on	amount and frequency of drug administration	duration of tafenoquine administration	protective efficacy in % (95% CI)
Lell 2000	410	5	pp	200 mg, only loading dose (taf)	3 days (primary endpoint at day 56) 3 days (secondary endpoint at day 77)	100 (0, 100) 100 (71, 100)
Shanks 2001	235	4	mITT	200 mg, weekly (taf) 400 mg, only loading dose (taf) 400 mg, weekly (taf)	13 weeks	86 (73, 93) 68 (53, 79) 89 (77, 95)
Hale 2003	509	6	mITT	200 mg, weekly (taf) 250 mg, weekly (mef)	12 weeks	85.6 (76.2, 91.6) 85.7 (71.9, 93.3)
Walsh 2004	205	2	mITT	400 mg, monthly (taf)	26 weeks	97 (82, 99)
Nasveld 2010/ Dow 2014*	651	2	pp/ITT	200 mg, weekly (taf) 250 mg, weekly (mef)	26 weeks	100 (93, 100)* 100 (79, 100)*
Stoute 2017	300	3	pp	200 mg, weekly (taf) 250 mg, weekly (mef)	24 weeks	77.9 (59.7, 88.2) 56.8 (32.5, 72.9) drug failure (%)
Brueckner 1998	6	2	ITT	600 mg, once (taf)	1 day	25
McCarthy 2018	16	2	ITT	200 mg, weekly (taf)	2 weeks	0

reported evidence for differences in nervous system AE or psychiatric AE between tafenoquine, placebo, and/or mefloquine groups (Figs. 8 and 9). However, the study published by McCarthy et al., 2018 with 16 participants reported more than twice as many nervous system AE in the placebo group than in the tafenoquine group (headache $n = 4/4$; 100.0% vs. $n = 4/7$; 57.1%, hypoesthesia $n = 1/4$; 25% vs. $n = 0/0$; 0.0%, respectively) [29]. Additionally, Leary et al., 2009 also reported more nervous system AE in the placebo group compared to the tafenoquine group (especially headache $n = 21/39$; 53.8% vs. $n = 29/81$; 35.8%, respectively) [28].

4. Discussion

This systematic review and meta-analysis assessed all available records to determine the efficacy and safety of tafenoquine as a chemoprophylactic drug against malaria. Tafenoquine chemoprophylaxis significantly protects from *P. falciparum* and possibly *P. vivax* infections with the approved dosage of weekly 200 mg. An adverse event incidence comparable to placebo or to mefloquine comparator was considered consistent with good safety and tolerability of tafenoquine chemoprophylaxis. We found an increased risk of gastrointestinal adverse events in tafenoquine arms and one study involving 6 months of dosing detected a significant increase in mild and reversible vortex keratopathy. Given the limited number of participants in the trials evaluated

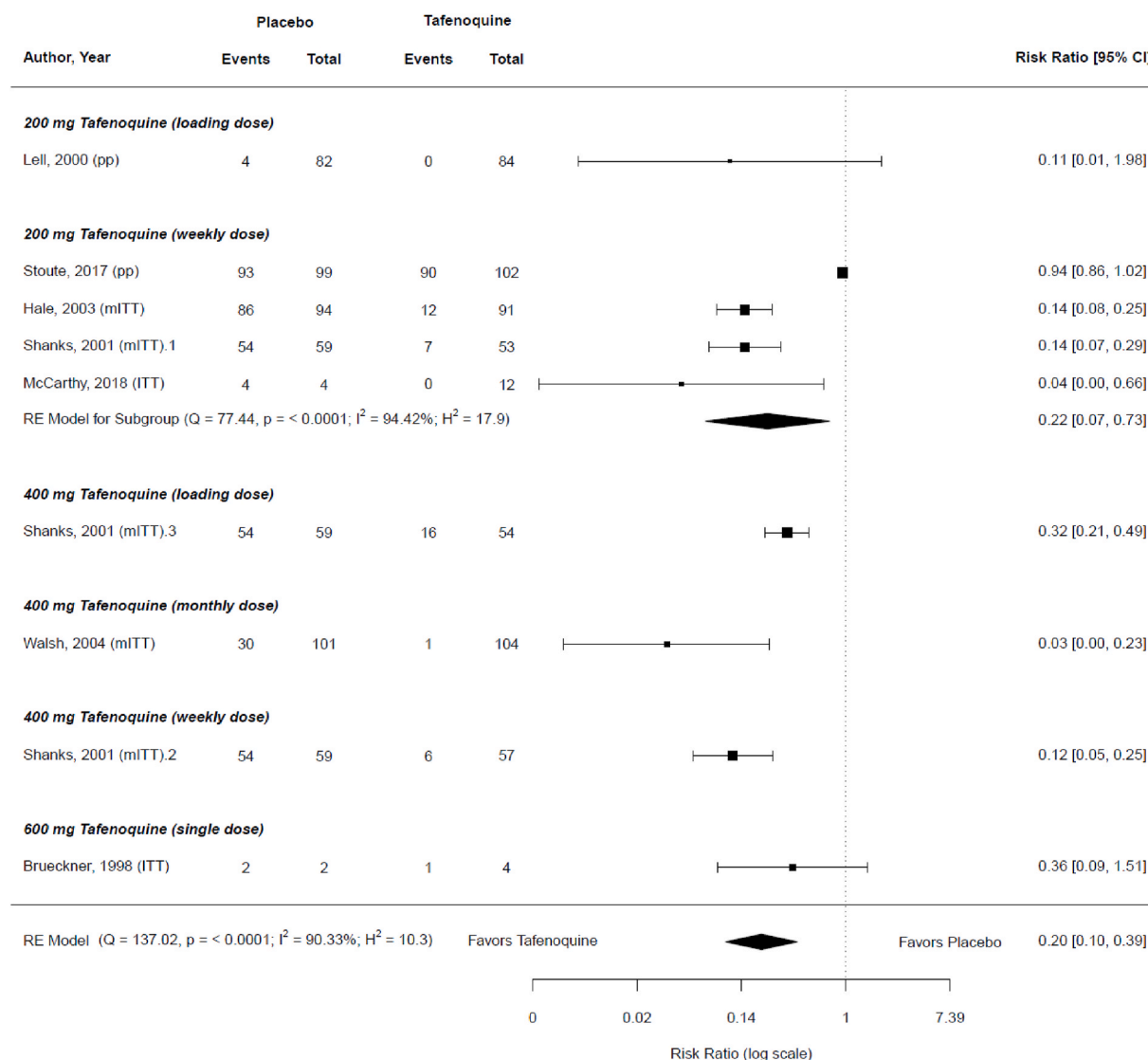


Fig. 6. Forest plot of tafenoquine versus placebo. Pooled RR for 200 mg tafenoquine = 0.22 (95%-CI: 0.07–0.73; p = 0.013); Pooled RR for all tafenoquine doses = 0.20 (95%-CI: 0.10–0.39; p < 0.0001). For Lell et al., 2000, only the primary endpoint for efficacy (day 56) was analysed, thus, only that data is displayed here.

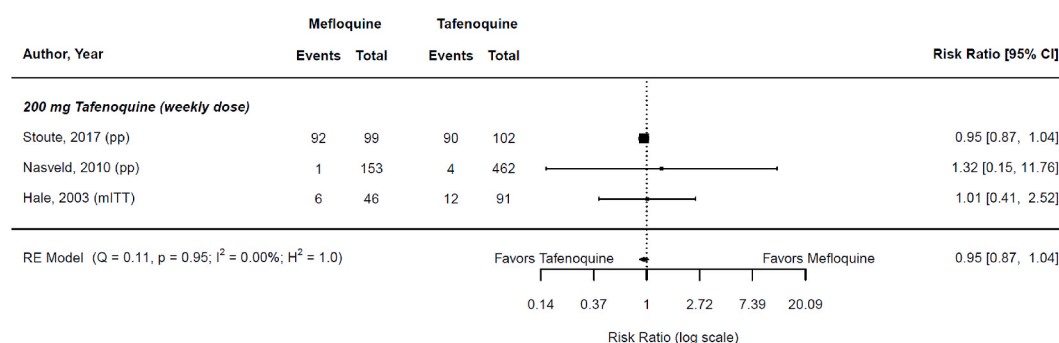


Fig. 7. Forest plot of tafenoquine vs mefloquine. Pooled RR = 0.95 (95%-CI: 0.87–1.04; p = 0.26).

here, we may not rule out relatively infrequent or rare serious adverse events detectable only in larger post-marketing studies.

Regarding efficacy, our analysis shows that the currently approved prophylactic dosage of weekly 200 mg tafenoquine significantly protects against *P. falciparum* (RR = 0.22; 95%-CI: 0.07–0.73; p = 0.013). In two of these analysed studies, a protection against *P. vivax* was also seen. One study did not show any advantage in taking tafenoquine for

chemoprophylaxis, but an Independent Data Monitoring Committee (IDMC) identified numerous false positive malaria microscopy readings. That trial cannot therefore be considered an accurate measurement of the chemoprophylactic efficacy of tafenoquine [36]. However, we included the afore-mentioned study to give a complete view of tafenoquine chemoprophylaxis and to avoid publication bias. Beside weekly 200 mg tafenoquine, other dosages also showed statistically

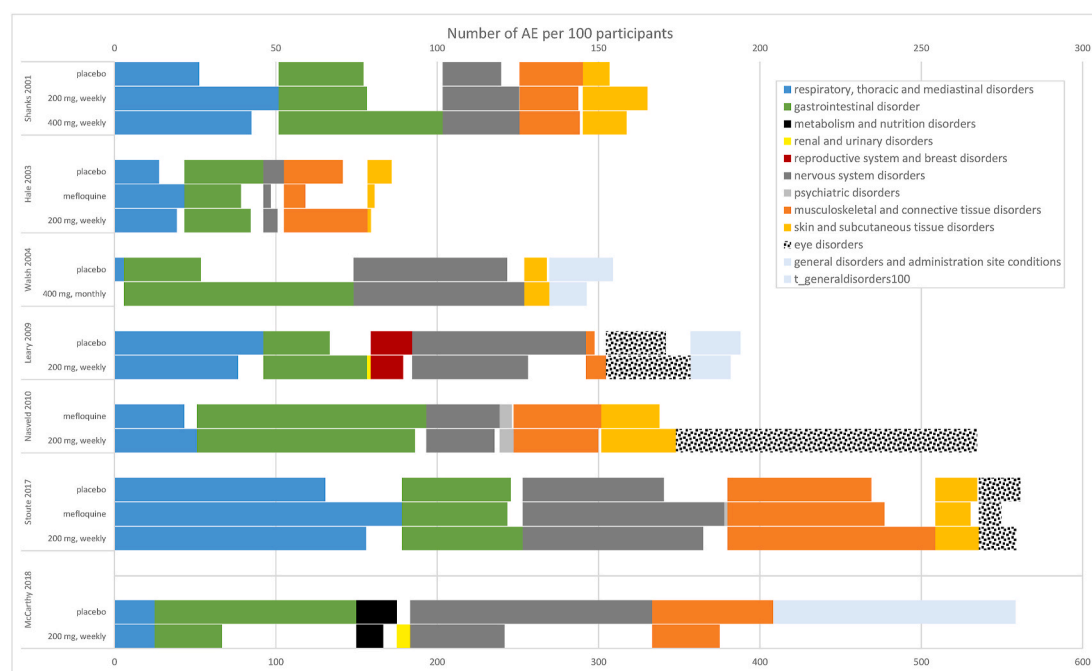


Fig. 8. Overview of all reported adverse events per 100 participants grouped with MedDRA® terms. The bars represent the numbers of AE and the labelled x-axis gives the participant range. Groups with less than 5% as well as the MedDRA® group “injury, poisoning and procedural complications” are not displayed. Due to differences in adverse events reporting, comparisons between absolute number of adverse events should only be made within a study. All AE were counted, therefore one person could have more than one headache. Nasveld et al., 2010, Leary et al., 2009, Stoute et al., 2017 and Shanks et al., 2001 only published adverse events when they occurred in at least 5% of the subjects in any treatment group, serious adverse events were an exception [28,32,34,38].



Fig. 9. Overview of all reported adverse events per 100 participants, grouped in MedDRA® terms with colour. The bars represent the numbers of AE and the labelled x-axis gives the participant range. AE with less than 5% as well as “injury” and “others” are not displayed. Due to differences in adverse events reporting, comparisons between absolute number of adverse events should only be made within a study. All AE were counted, therefore one person could have more than one headache. Nasveld et al., 2010, Leary et al., 2009, Stoute et al., 2017 and Shanks et al., 2001 only published adverse events when they occurred in at least 5% of the subjects in any treatment group, serious adverse events were an exception [28,32,34,38]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

significance: monthly and weekly 400 mg tafenoquine as well as a 400 mg loading dose (400 mg 3 times over 3 days) for 13 weeks with a follow-up of 4 weeks in a *P. falciparum* endemic region; whereas a 200 mg tafenoquine loading dose (200 mg, 3 times over 3 days) and a single 600 mg dose did not yield a significant protective effect (Fig. 6). No

evidence for a difference in efficacy between tafenoquine and mefloquine was detected. However, the compared populations with 655 and 298 participants, respectively, are too small to make a definitive conclusion with regard to the non-inferiority of efficacy of one in regard to the other. Nonetheless, tafenoquine might be considered more often

Table 6

Overview of all adverse events displayed as number per 100 participants.

	Study	Shanks 2001	Hale 2003	Walsh 2004	Leary 2009	Nasveld 2010	Stoute 2017	McCarthy 2018
	participants for safety analysis (n)	235	513	205	120.00	654	306	16
	Analysis based on	mITT	mITT	mITT	mITT	mITT	ITT	ITT
placebo	AE	n = 60/61; 98.4%	n = 91/94; 96.8%	n = 105/101; 104%	n = 61/39; 156.4%	NA	n = 251/101; 248.5%	n = 22/4; 550%
	serious AE	n = 2/61; 3.3%	n = 1/94; 1.1%	n = 7/101; 6.9%	n = 3/39; 7.7%	NA	n = 5/101; 5%	n = 0/4; 0%
	related serious AE discontinued	n = 0/61; 0% n = 7/61; 11.5%	n = 0/94; 0% NR	NR n = 9/101; 8.9%	n = 0/39; 0% n = 4/39; 10.3%	NA NA	NR n = 2/101; 2%	n = 0/4; 0% n = 0/4; 0%
	discontinued due to AE	n = 0/61; 0%	n = 3/94; 3.2%	n = 0/101; 0%	n = 2/39; 5.1%	NA	n = 0/101; 0%	n = 0/4; 0%
250 mg mefloquine (weekly)	AE	NA	n = 34/46; 73.9%	NA	NA	n = 328/162; 202.5%	n = 293/101; 290.1%	NA
	serious AE	NA	n = 0/46; 0%	NA	NA	NR	n = 2/101; 2%	NA
	related serious AE discontinued	NA	n = 0/46; 0% NR	NA	NA	NR	NR	NA
	discontinued due to AE	NA	n = 0/46; 0%	NA	NA	n = 9/162; 5.6%	n = 2/101; 2%	NA
400 mg tafenoquine (monthly)	AE	NA	NA	n = 148/104; 142.3%	NA	NA	NA	NA
	serious AE	NA	NA	n = 1/104; 1%	NA	NA	NA	NA
	related serious AE discontinued	NA	NA	NR n = 8/104; 7.7%	NA	NA	NA	NA
	discontinued due to AE	NA	NA	n = 0/104; 0%	NA	NA	NA	NA
200 mg tafenoquine (weekly)	AE	n = 77/55; 140%	n = 102/93; 109.7%	NA	n = 113/81; 139.5%	n = 1043/492; 212%	n = 319/104; 306.7%	n = 25/12; 208.3%
	serious AE	n = 1/55; 1.8%	n = 2/93; 2.2%	NA	n = 8/81; 9.9%	NR	n = 10/104; 9.6%	n = 0/12; 0%
	related serious AE discontinued	n = 0/55; 0%	n = 0/93; 0%	NA	n = 1/81; 1.2%	NR	NR	n = 0/12; 0%
	discontinued due to AE	n = 14/55; 25.5%	NR	NA	n = 9/81; 11.1%	n = 30/492; 6.1%	n = 2/104; 1.9%	n = 0/12; 0%
400 mg tafenoquine (weekly)	AE	n = 1/55; 1.8%	n = 9/93; 9.7%	NA	n = 6/81; 7.4%	n = 12/492; 2.4%	n = 0/104; 0%	n = 0/12; 0%
	AE	n = 88/59; 149.2%	NA	NA	NA	NA	NA	NA
	serious AE	n = 2/59; 3.4%	NA	NA	NA	NA	NA	NA
	related serious AE discontinued	n = 0/59; 0% n = 12/59; 20.3%	NA	NA	NA	NA	NA	NA
	discontinued due to AE	n = 0/59; 0%	NA	NA	NA	NA	NA	NA

as chemoprophylaxis if future safety data and a lower intake frequency support the use of tafenoquine over mefloquine.

Our initial goal was to provide a meta-analysis of safety, but this was not feasible as individual safety data were not available. According to our safety analysis, gastrointestinal disorders were the most frequent adverse events (Fig. 9). A significantly higher occurrence of adverse events in the tafenoquine arms was only reported in one study for gastrointestinal disturbances and in another for vortex keratopathy. Even though some adverse events trended higher, relatively small study populations limited statistical power and inference. The frequency of discontinuation of dosing varied greatly but was mostly low, especially considering the relatively long durations involved in these trials (Tables 5 and 6). The trial from western Kenya reported by Shanks et al., 2001, however, seemed to have had a relatively high discontinuation rate not addressed by those authors. Nevertheless, no evidence for a difference in study discontinuation between arms was reported in any trial. Since some of the trials employed military personnel as subjects, where a culture of discipline typically occurs, an expectation of similarly good adherence among more ordinary travellers should be regarded with some caution. Nonetheless, weekly dosing should favour good adherence.

Ophthalmological adverse events are important in safety assessments

of tafenoquine because Nasveld et al., 2010 detected vortex keratopathy events in most subjects exposed to tafenoquine chemoprophylaxis for 6 months. Leary et al., 2009 [28]. Did a thorough study of ophthalmic safety over a prolonged period and reported a trend towards vortex keratopathy. Neither trial detected visual disturbances. Other ophthalmic safety studies were conducted employing other dosing regimens [39–42]. Among those, Warrasak et al., 2018 [40] showed 400 mg daily TQ for 3 days caused mild vortex keratopathy. However, that ophthalmic safety assessment was inadequately statistically powered [40]. Tafenoquine causing vortex keratopathy may be apparent but is not yet definitive due to differences in ophthalmologic assessment methods and variable exposure to UV light depending on study location [28,43]. Vortex keratopathy is known to be associated with several drugs which are taken over a longer period (e.g. amiodarone) and usually does not interfere with visual acuity and is usually reversible, but can be associated with advanced retinopathy [44]. Retinal changes were also assessed in randomized participants by three studies where no evidence for differences to placebo was detected, however, Leary et al., 2009 reported a mild decrease in macular sensitivity which resolved spontaneously [28,39,40]. Although ophthalmic adverse events caused by tafenoquine appear mild, they should not be dismissed because conclusive data has yet to be developed. Notably the 4-aminoquinoline

Table 7

Laboratory adverse events.

	Abnormal haemoglobin and haemolysis parameters	Bilirubin	Liver enzymes	Kidney parameters	methaemoglobin
Shanks 2001	Shanks et al., 2001 recorded haemolytic events in two subjects; however, their G6PD status had been incorrectly determined identified during screening.	NR	NR	NR	A mean plateau concentration for weekly 200 mg tafenoquine of $2.5\% \pm 1.6\%$ (SD) and for weekly 400 mg of $4.5\% \pm 2.5\%$ (SD) was reported.
Hale 2003	Decreased haemoglobin cases (<8.0 g/dl): •placebo: 1/94 (1.06%) •tafenoquine 25 mg: 2/93 (2.2%) •tafenoquine 50 mg: 2/93 (2.2%) •tafenoquine 200 mg: 3/93 (3.2%)	NR	elevated ALT levels (61.9–193 U/L •placebo: 2/94 (2.1%), •tafenoquine 25 mg: 4/93 (4.3%) •tafenoquine 50 mg: 4/93 (4.3%) •tafenoquine 100 mg: 7/94 (7.4%) •tafenoquine 200 mg: 6/93 (6.5%) All elevated ALT levels were not dose- or weight-related. According to the study authors: “Nearly every subject, irrespective of study arm, experienced a notable, predominantly mild elevation in ALT level from baseline to week 4 that progressively diminished [...] to the end point. Subjects with abnormally elevated ALT levels improved and/or their ALT levels normalized after cessation of tafenoquine therapy.	NR	NR
Walsh 2004	NR	NR	Elevated ALT levels (>70 U/L): •placebo: 5/101 (5.0%), tafenoquine 7/104 (6.7%) The highest ALT values were caused by a chronic hepatitis B infection. All elevated ALT levels were transient and not associated with symptoms.	Elevated serum creatinine: •tafenoquine 400 mg: 11/104 (10.6%) •placebo 3/101 (3.0%) All elevated creatinine levels were transient, occurred between the loading and the first monthly dose and returned to normal by the second month dose. Elevated serum creatinine (≥ 26.6 μ mol/L from baseline): •placebo: 1/32 (3.1%) •tafenoquine 200 mg: 3/70 (4.3%) Those elevated serum creatinine values were interpreted as clinically important but were not associated with clinically significant decreases in GFR. Non-inferiority was found between tafenoquine 200 mg and placebo concerning GFR.	Elevated methaemoglobin levels ($\geq 3.0\%$): •tafenoquine 400 mg: 23/104 (22.1%) A maximum value of 6.9% was reported.
Leary 2009	Decrease in haemoglobin, haptoglobin and haematocrit: •Tafenoquine 200 mg: 1/81 (1.2%). Resolved itself after tafenoquine withdrawal. A “higher incidence of mild reductions in haptoglobin ($<85\%$ baseline) in the tafenoquine group compared with the placebo group (47% versus 31%)” and a higher incidence of increased reticulocytes ($\geq 150\%$ baseline) in the tafenoquine group from week 3–12, but not in week 12–24” was reported.	NR	NR	Elevated serum creatinine (≥ 26.6 μ mol/L from baseline): •placebo: 1/32 (3.1%) •tafenoquine 200 mg: 3/70 (4.3%) Those elevated serum creatinine values were interpreted as clinically important but were not associated with clinically significant decreases in GFR. Non-inferiority was found between tafenoquine 200 mg and placebo concerning GFR.	NR
Nasveld 2010	Decreased haematocrit cases: •mefloquine: 23/162 (14.2%) •tafenoquine 200 mg: 98/492 (20.0%) with two (0.4%) clinically significant cases ($<85\%$ of the lower limit of normal range)	Increased bilirubin (>2 μ mol/L above from the baseline) •tafenoquine 200 mg: 49/492 (10.0%) •mefloquine: 5/162 (3.1%) clinically significant increased bilirubin ($>150\%$ of the upper limit of normal ranges) •tafenoquine 200 mg: 13/492 (2.6%) •mefloquine: 1/162 (0.6%)	NR	elevated serum creatinine ($>125\%$ baseline value) •tafenoquine 200 mg: 93/492 (18.9%) •mefloquine: 16/162 (9.9%) Those values were not considered clinically significant.	NR

(continued on next page)

Table 7 (continued)

	Abnormal haemoglobin and haemolysis parameters	Bilirubin	Liver enzymes	Kidney parameters	methaemoglobin
Stoute 2017	Haemolytic anaemia: • tafenoquine 200 mg: 1/104 (1.0%)	NR	NR	NR	NR
McCarthy 2018	Decrease in haemoglobin: • tafenoquine 200 mg: 2/12 (16.7%) Both cases were interpreted as not clinically significant and they resolved without treatment.	Hyperbilirubinemia (29.0 μ mol/L) in one participant of the tafenoquine group, which resolved spontaneously.	NR	NR	NR

called chloroquine is known to cause a vortex keratopathy which can result in irreversible retinopathy and even progression after drug cessation [44]. It is advisable to avoid prolonged tafenoquine co-medication with other vortex keratopathy-causing drugs such as amiodarone. Ophthalmological examinations might be considered before, during and/or after tafenoquine intake for lengthy periods of several months, especially if additional co-factors like already existing visual disturbances and/or monocular vision is present. For a definitive conclusion, ongoing evaluation is indicated.

No evidence for changes in nervous system or psychiatric AE were observed in the analysed trials compared to other treatment arms or placebo. Some events such as headache were reported more often in placebo recipients (Fig. 9) [28,29]. The molecular structures of primaquine and tafenoquine appear to eliminate the severe irreversible neurotoxicity observed in rhesus monkeys with other 8-aminoquinolines, specifically those having less than 4 methyl groups separating the primary and terminal amines of the aliphatic side chain [9,45]. Tafenoquine studies with rhesus monkeys showed no neurological signs that had been reported with those other 8-aminoquinolines at comparable dosages [9]. Furthermore, a tafenoquine study in rats showed, that other adverse events than neurotoxicity were dose-limiting [46]. Nonetheless, unspecified 8-aminoquinoline neurotoxicity may occur in patients having pre-existing nervous system or psychiatric disorders. Such patients have been excluded from trials of tafenoquine and regulators express caution regarding exposing them to tafenoquine (Appendix B) [9].

Quinolines and structurally related antimalarial drugs are known to have clinically relevant cardiovascular effects due to delay in ventricular depolarisation or QT prolongation [47]. No cardiac disorders were reported in our systematic review, and a recent publication that focused on QTc changes after single dose tafenoquine, detected no clinically meaningful effect on cardiac repolarization [48].

Several instances of diminished haemoglobin in G6PD-normal participants were reported, but only two cases of acute haemolytic anaemia occurred in G6PD-deficient subjects incorrectly identified as normal [38]. As is the case with other 8-aminoquinolines [19], G6PD screening is required to prevent potentially serious harm. In 2017, a single dose study showed that tafenoquine had similar haemolytic effects compared to 14 days of 15 mg primaquine base daily in healthy female volunteers heterozygous for mildly sensitive Mahidol variant of G6PD deficiency [49].

Clinically relevant elevation of bilirubin often occurred in tafenoquine recipients but was not more frequent than the same in those receiving placebo [33,37]. Elevated bilirubin levels can have several origins (e.g. haemolysis). However, no evidence for differences between study groups in liver enzymes or other haemolytic parameters were detected. The transient elevation of ALT, haemoglobin, and white blood cell (WBC) counts in all arms, reported by Hale et al., 2003, were interpreted as a result of the radical cure regimen at the beginning of the study [33]. The same conclusion might be made for the more common transient reduction of haptoglobin and increased reticulocytes reported in tafenoquine arms by Leary et al., 2009. However, those transient

blood parameters might also be due to the destruction of naturally G6PD-diminished senescent erythrocytes by tafenoquine [50].

Other laboratory parameters that showed a trend for abnormal values in tafenoquine groups were serum creatinine and methaemoglobin, but no evidence for differences to other study groups were reported. Creatinine levels are a fairly insensitive marker and in drug trials, cystatin c may serve as a more appropriate, highly sensitive marker of early renal dysfunction in future studies [51]. Tafenoquine, like all 8-aminoquinolines evaluated at therapeutic doses, causes methaemoglobin levels to rise slightly or moderately (typically 2–8% of Hb). This is of minor concern in normally dosed patients, however, an overdosage could lead to clinically relevant methaemoglobin concentrations (>20%) [52,53]. Even though serum creatinine changes were observed, Leary et al., 2009 showed by direct measuring of GFR, that renal functions were not impaired [28].

Another antimalarial drug, mefloquine, is known to attain higher plasma levels in female subjects compared to males. It has been conjectured that this may explain the higher incidence of mefloquine associated adverse events in women [54,55]. Conclusive data for sex differences in plasma drug levels during prolonged tafenoquine exposure are unavailable because most tafenoquine studies have been dominated by male subjects. However, Hale et al., 2003 detected evidence for an interaction between treatment efficacy and body weight ($P < 0.001$), which could play an incidental role in sex differences, should those be observed. A single dose tafenoquine safety study reported more adverse events in female participants, however a review including 6 single-dose tafenoquine studies concerning population pharmacokinetics concluded that sex, ethnicity, or age did not impact on safety [16, 56]. Charles et al., 2007 analysed the population pharmacokinetics of the population from Nasveld et al., 2010 and concluded that measured tafenoquine concentrations in that study are not the primary predictor of tafenoquine tolerability. However, since the analysed population consisted of homogenous military personal (Table 1) pharmacokinetics in overweight or underweight may still require dose adjustments [14]. A similar conclusion was published by Edstein et al., 2001, concerning a population of Thai soldiers [37].

This systematic review with meta-analysis combines data to estimate efficacy and adverse events/safety with more accuracy than a single study. However, there are limitations to consider, mainly several differences in population characteristics, a limited population size for detecting rare adverse events, inclusion of healthy people only (Appendix B), low numbers of women, risk of bias, and differences in adverse events reporting (Table 4).

The populations differed in ethnicity, nutritional status, culture, employment (e.g. military) stress levels (e.g. peacekeeping operation in East Timor [19]), tolerance of medications, semi-immunity, and varying degree of female/male ratios. This population heterogeneity makes it difficult to compare absolute numbers between single studies, especially for adverse events reporting [57]. The differences in study design between longitudinal trials and human challenge studies limit their comparability, since human challenge studies have fewer participants and a guaranteed exposure rate of 100%.

The low portion of female participants restrict prediction of adverse events in women. It has already been described that mefloquine is associated more often with neuropsychological adverse events in women compared to men [58]. This would also explain the missing higher incidence of neuropsychological adverse events in all 3 RCT's with mefloquine arms (female portion $n = 303/1463$; 20.7%).

Since pregnant or breast-feeding women, children, G6PD-deficient, and those with psychiatric disorders, neurological disorders, abnormal laboratory results and/or clinical examinations were all excluded (App. B), the conclusion for safety and efficacy in this systematic review is restricted to the included participants and may not accurately or reliably apply to populations of travellers that may include these groups, unintentionally or otherwise. The strengths of our meta-analysis are the inclusion of well conducted randomized studies, most with a low risk of bias, the stringent selection criteria used in our methodology and the thorough statistical analyses performed.

5. Conclusion

Between 1998 and 2018, nine randomized, controlled studies concerning tafenoquine chemoprophylaxis efficacy and safety were published. Our systematic review and meta-analysis of these studies indicates that weekly tafenoquine 200 mg regimens are well tolerated and effective as malaria chemoprophylaxis focusing primarily on *Plasmodium falciparum* but also on *Plasmodium vivax*. An increased risk of gastrointestinal adverse events in the tafenoquine arms were reported by three studies, and one study detected a significant increase in reversible vortex keratopathy with 6 months of dosing. Most studies to date have been done in young adult and predominantly male populations. Further research is indicated on the use of tafenoquine in far more diverse traveller populations in order to detect rarer adverse events, sex differences in pharmacokinetics and tolerability in those with polymedication.

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CRediT authorship contribution statement

Julian D. Maier: Writing - original draft, Data curation, did the Prospero registration and conducted the literature searches, screened all papers, contacted study authors, and evaluated the risk of bias, compiled the tables, All co-authors contributed to, and endorsed, the final version of the manuscript. **Sandra Siegfried:** Methodology, Formal analysis, All co-authors contributed to, and endorsed, the final version of the manuscript. **J. Kevin Baird:** advised on study design, interpretation, context, and gave input to the manuscript, All co-authors contributed to, and endorsed, the final version of the manuscript. **Martin P. Grobusch:** advised study design, interpretation, context, and gave input to the manuscript, All co-authors contributed to, and endorsed, the final version of the manuscript. **Patricia Schlagenhauf:** Writing - original

draft, Data curation, designed the study, screened all papers, contacted study authors, and evaluated the risk of bias, All co-authors contributed to, and endorsed, the final version of the manuscript.

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Appendix A. Supplementary data

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